

Fifth Quarterly Progress Report
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**The Neurophysiological Effects of
Simulated Auditory Prosthesis
Stimulation**

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1 Introduction

In this contract, we are using experimental and computer models to investigate issues relevant to electrical stimulation the auditory nerve. In addition to studying basic response properties of the nerve, we are also examining possible means of enhancing the transfer of information from implanted electrodes to auditory nerve fibers.

We have used several measures of the electrically evoked compound action potential (EAP) to characterize important properties in auditory nerve fiber response that may be most relevant to stimulus coding in prosthetic devices. Basic threshold and amplitude-level (i.e., growth) characteristics are important in relation to changes in stimulus intensity. Two-pulse (masker-probe) stimulus paradigms provide a means of characterizing temporal interactions that occur when the nerve is placed in a refractory state by a prior stimulus. More complex stimuli, such as pulse trains and modulated pulse trains, are used to examine both short-term and long-term adaptation effects. Such pulse trains provide stimulus conditions more representative of the regimens used in current designs of auditory prostheses. Finally, we measure channel interaction effects to assess the independence of information transmitted on different electrodes of a multi-electrode array. We view the close coupling of computer model simulations and physiologic recordings as a key feature of this project. These parallel approaches are used to both measure and simulate the EAP of the auditory nerve as well as responses of single auditory nerve fibers.

2 Activities of the Fifth Quarter

- We continued single unit and EAP recordings for both monophasic and biphasic stimuli in five acutely deafened cats.
- We have studied electrode interaction effects at both single-unit and EAP level for two multielectrode designs in four cats.
- We have preliminary data on the effects of spiral ganglion cell loss on EAP growth functions in the cat.
- In six guinea pigs we have studied the effects of high rate pulse trains and additive noise on EAP responses.
- We have continued EAP studies of amplitude modulated pulse trains.

- We have completely characterized a new phenomenon of electrical stimulation in simulated fibers: pseudospontaneous activity. A manuscript has been completed describing these findings, but its submission has been delayed pending a patentability study. The nature and potential importance of pseudospontaneous activity will be the topic of this quarterly progress report.

3 Pseudospontaneous Activity

3.1 Background

A major difference between the deaf and hearing ears is the relative absence of spontaneous activity in the deafened cochlea[5, 7]. This has implicated the inner hair cell synapse as the source of spontaneous activity[11] although recently it has been suggested that elimination of spontaneous activity with ototoxic deafening is not as complete as might be suspected[12]. We expect that restoration of physiologic levels of spontaneous activity to the deafened cochlea would be a productive approach to speech processor design for a number of reasons:

- The normal auditory nerve is spontaneously active in quiet[6]. Sound produces a slowly progressive within and across fiber synchronization as intensity is increased[10]. Replication of this phenomenon should allow greater dynamic range and more orderly loudness growth.
- Studies of “stochastic resonance” demonstrate increased temporal resolution in sensory systems when independent noise is present in a set of parallel detectors[2]. The spiral ganglion is quite comparable to such parallel detectors and spontaneous activity in each fiber is a form of independent noise[4].
- Loss of spontaneous activity is one proposed mechanism for tinnitus[5] and its restoration may potentially improve tinnitus suppression by cochlear implants.

We have investigated a number of possible approaches to increasing stochastic independence in responses of auditory nerve fibers to electrical stimulation. The first is to employ the pulse rate that maximizes the stochastic properties of the refractory period. We have demonstrated in models and measures of the electrically-evoked compound action potential (EAP) that

an interpulse interval between 0.9 and 1.0 ms substantially decreases the slope of the neural input-output function and EAP growth function[8]. This is due to a dramatic increase in the noise of the voltage-sensitive sodium channel during the relative refractory period[9]. While promising, this interesting effect is exquisitely sensitive to the interpulse interval. Any channel interactions present in a cochlear implant could make it difficult or impossible to control the interpulse interval “seen” by a given neural population.

A second approach is to modulate high rate pulse trains with the envelope of the filtered, compressed speech signal. At low rates, amplitude of the EAP to successive pulses in the train show an alternating pattern – suggesting refractory effects which are evident due to the high degree of synchronization[14, 1]. At high rates, above 2 kHz in humans, the response amplitudes are constant after the first few pulses indicating an increased stochastic independence of the firing patterns of the fiber population[14]. This approach requires modulation of very high rate stimuli and produces small compound action potentials suggesting that small numbers of fibers are available (not absolutely refractory) at any time. Representation of temporal details of the speech envelope would benefit from maintenance of these high levels of stochastic independence, but increasing the available fiber pool that is not absolutely refractory.

A third approach, the topic of this work, is to attempt to recreate the independent noise source found naturally in normal auditory nerve fibers. We have found that spike trains can be produced in simulated electrically-activated auditory nerve fibers that have statistical properties similar to spontaneous activity in normal spiral ganglion cells. We call this “pseudospontaneous” activity.

3.2 Results

3.2.1 Supercomputer simulations

Figure 1 demonstrates the post-stimulus time (PST) histogram of the fiber model with a stimulus amplitude of $325 \mu\text{A}$. There is a highly synchronous response to the first, higher amplitude pulse. This is followed by a “dead time”, then an increased probability of firing followed by a fairly uniform firing probability. There is a small degree of periodicity with the stimulus as measured by a vector strength[3] of 0.26.

Figure 1 also demonstrates the interval histogram of the same spike train. It illustrates a dead time, followed by a rapid increase in probability, followed

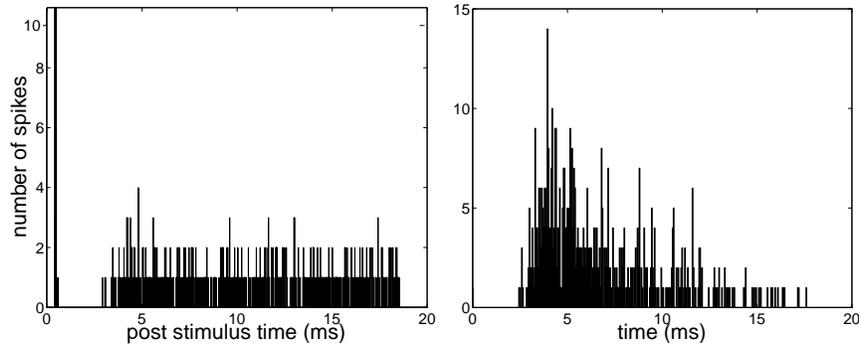


Figure 1: PST and ISI histograms of model response to 5 kHz pulse train at $325 \mu\text{A}$. The y-axis of the PST histogram has been scaled to demonstrate the temporal details following the highly synchronous response to the first pulse.

by an exponential decay. This interval histogram is thus consistent with a Poisson process following a dead time, a renewal process, and greatly resembles that seen with spontaneous activity in the intact auditory nerve. This response corresponds to a spontaneous rate of 116 spikes/second measured during the uniform response period of 7 to 17 ms.

If the stimulus intensity is varied, the firing rate and shape of the PST and interval histograms change. Figure 2 illustrates four interval histograms at different stimulus intensities demonstrating a range of possible firing rates. The interval histograms change shape with changes in pseudospontaneous rate in a manner consistent with normal auditory nerve fibers. All demonstrate Poisson-type intervals following a dead-time.

Figure 3 demonstrates the conditional mean histogram and hazard function for a single “unit” simulated for eight seconds. The conditional mean histogram falls within the theoretical standard deviations and thus is “constant”, consistent with a renewal process[4]. This indicates that firing probability is not affected by intervals prior to the previous spike. The hazard function is also “constant” at least for the intervals for which eight seconds is an adequate sample. The large fluctuations in the hazard function at long intervals are due to the small number of spikes in this “brief” simulation.

Given the statistical similarity of these electrically-evoked responses to spontaneous activity in the normal auditory nerve, these responses have been termed “pseudospontaneous activity”. Figure 4 demonstrates the rela-

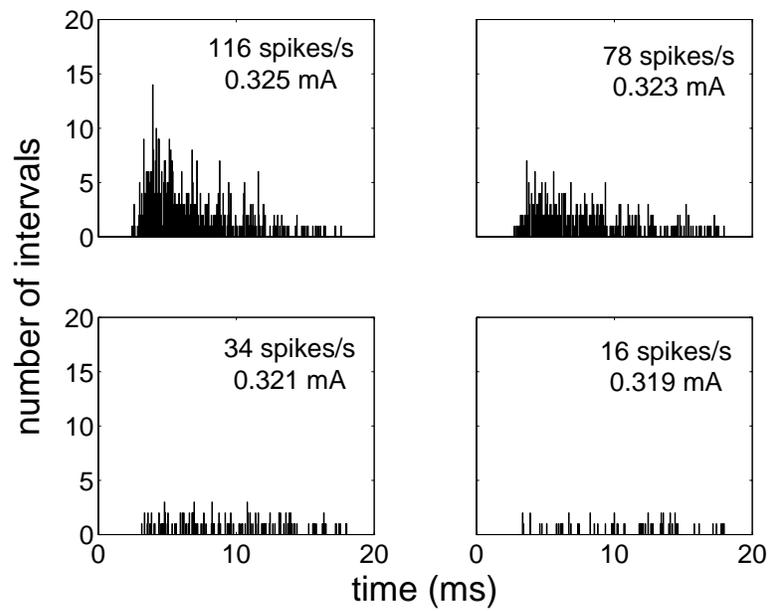


Figure 2: Interval histograms of model response to a 5 kHz pulse train at four stimulus intensities. The firing rate during the period of uniform response probability is given in the upper right corner of each plot.

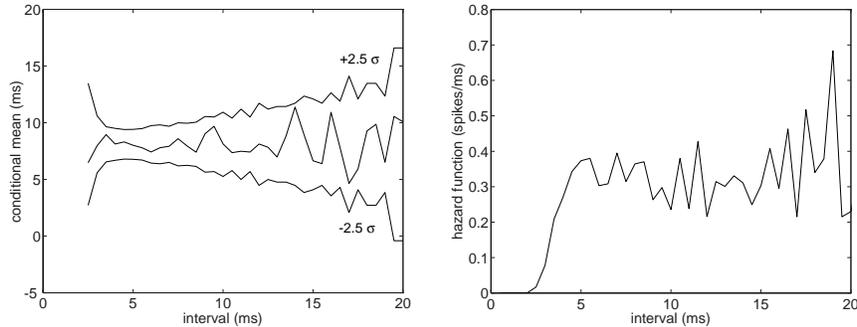


Figure 3: Conditional mean histogram and hazard function for a “unit” simulated for eight seconds. On the left, the conditional mean is plotted as well as theoretical limits of $\pm 2.5\sigma$ ($p < .012$). Since there are forty bins in the histogram, the calculations are consistent with a conditional mean that is “constant”. On the right is the hazard function which is consistent with a dead-time, followed by a rapidly rising function that is then “constant” within the limits of the small number of spikes simulated. Both plots are consistent with a renewal process much like spontaneous activity.

tionship between stimulus intensity and pseudospontaneous rate. It is clear that the full range of spontaneous rates seen in the cat cochlea can be simulated over a narrow range of stimulus intensity. As the model fibers are uniform, the true range of intensities in a real fiber population is likely substantially greater due to the four-fold range of electrical thresholds in the cat[13]. Practically this implies that at an appropriate stimulus intensity, a range of pseudospontaneous rates would be found if the nerve were properly sampled. Since there is minimal synchronization with the stimulus, compound action potentials in response to individual pulses would be expected to be small or unmeasurable.

Figure 5 illustrates PST and interval histograms for two “high intensity” stimuli which produce firing rates well above those considered physiologic for spontaneous activity. The PST histograms indicate a progressive locking of the responses to the refractory period and the interval histograms demonstrate a shortening of the refractory period as the stimulus increases. Of note, at these intensities, there is no periodicity with the stimulus (vector strength is zero). These patterns make intuitive sense as at these high levels, spike times are determined strictly by the time of the end of the relative refractory period. This time would be expected to shorten as stimulus

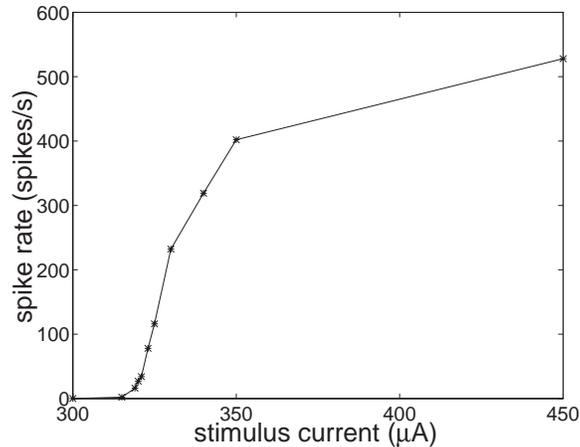


Figure 4: Simulated relation between stimulus intensity and pseudospontaneous rate.

intensity increases.

Normal spontaneous activity is independent across neurons and the best proof of fiber independence is the recurrence-time test[4]. Measurement of recurrence-time histograms requires simulations of long spike trains. Johnson and Kiang recorded from two fibers simultaneously for 100 seconds to apply this technique — a duration well beyond reasonable application of current supercomputer hardware and algorithms. By increasing the bin size to 0.5 ms, useful recurrence-time histograms could be assembled from two 2 second spike trains.

Figure 6 demonstrates a 50 ms recording of the two simulated neurons and the ISI histogram of an eight second run from one of them. The forward recurrence-time histogram of the two “units” and the theoretical forward recurrence-time calculated assuming the “units” are independent[4] are also shown. The theoretical curve is flat during the refractory period. The residual calculated by subtracting the theoretical and measured recurrence-times is shown in the bottom panel. By the central limit theorem, the residuals have a Gaussian distribution and the theoretical limits of the residuals are plotted at $p < .0124$ (2.5 standard deviations). Thus in this 80 bin histogram, the residuals should exceed the limits more than one or two times if the spike trains are not independent.

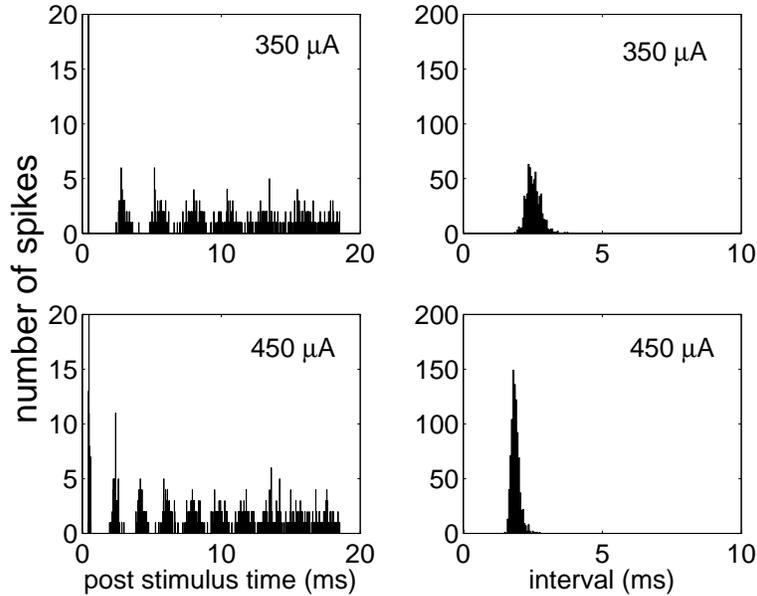


Figure 5: PST and interval histograms at “high” stimulus intensities.

3.2.2 EAP recordings

Figure 7 demonstrates the EAP N1P2 magnitude from a human subject with a “low rate” stimulus of 1 kHz and a “high rate” stimulus of 3 kHz. The low rate response demonstrates the typical alternating pattern that has been extensively described elsewhere[14]. This pattern arises due to the refractory period of the nerve and might be expected to degrade the neural representation of the stimulus envelope. With the first stimulus, a large response occurs presumably due to synchronous activation of a large number of fibers. These fibers are subsequently refractory for the second pulse which then generates a small response. By the time of the third pulse, an increased pool of fibers becomes available and the response increases. The alternating pattern then continues indefinitely in several human subjects[14]. Many variations on this alternating pattern have been identified in model simulations and animal studies[1].

The high rate curve demonstrates a large response followed by a period of transiently depressed excitability, followed by a constant EAP amplitude. This result should be compared with the simulation in Figure 1. It is apparent that the constant response amplitude after 1 ms in Figure 7 must be

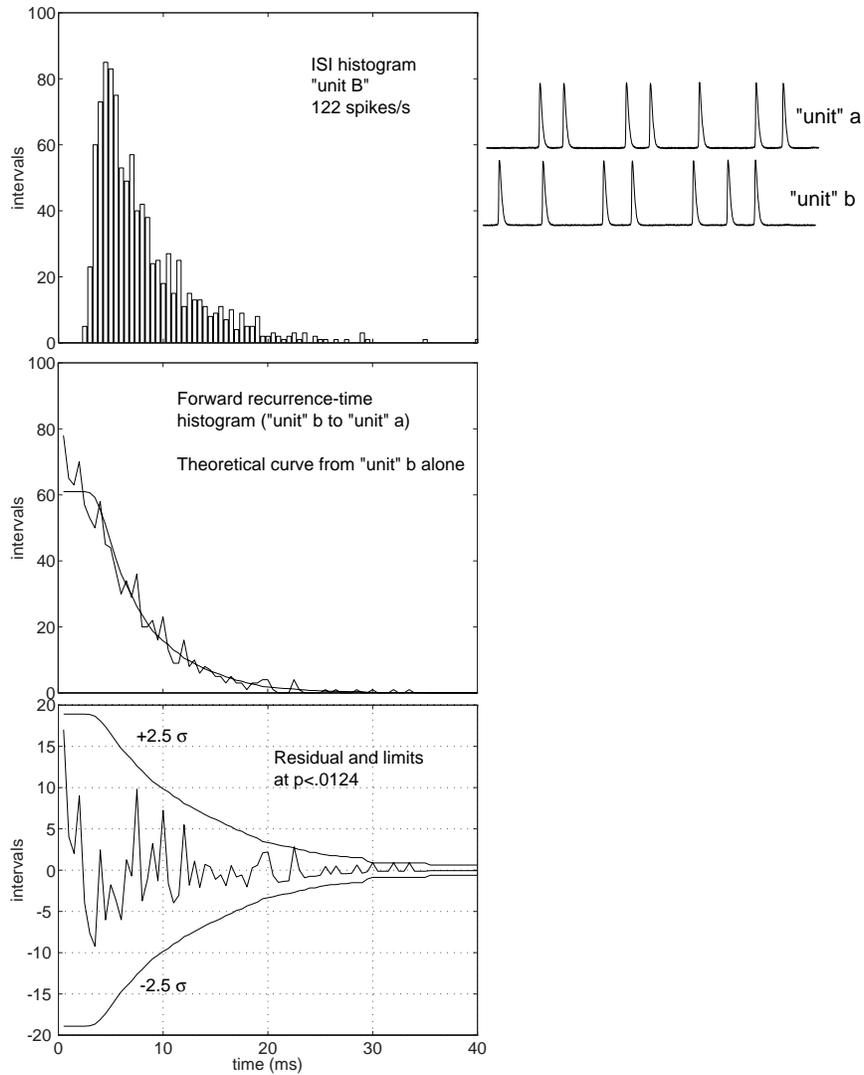


Figure 6: The upper right panel shows a 50 ms sample of spike activity from the two “units”. The upper left panel shows the ISI histogram from “unit” b. The middle panel shows the forward recurrence time histogram of “unit” b to “unit” a as well as the theoretical recurrence-time from unit b assuming that “units” a and b were independent. The lowest panel shows the residuals calculated by subtracting the curves in the middle panels. Also shown are the theoretical limits at $p < .012$. For mathematical details, see Johnson and Kiang, 1976.

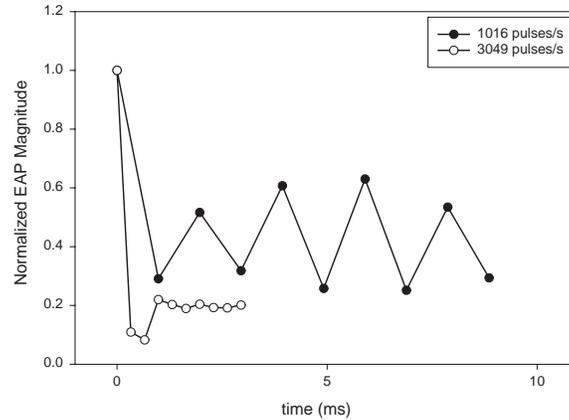


Figure 7: EAP N1P2 magnitudes from a human subject with 1.016 and 3.049 kHz constant pulse train stimuli. Responses are normalized to the response to the first pulse. Note that the higher rate stimulus produces a flat response magnitude after 1 ms. Compare the 3.049 kHz curve with the simulated PST histogram in Figure 1. Courtesy of Blake Wilson and Charles Finley.

due to a different, likely equal sized, pool of fibers responding to each pulse. This phenomenon is almost certainly the EAP manifestation of stochastic independence at the single-unit level as suggested by our simulations.

If pseudospontaneous activity can be created by a high-rate constant pulse train, it ought to be possible to desynchronize the auditory nerve using such a stimulus. This desynchronization would have obvious benefits for temporal representation of a modulated stimulus, but also would make the responses more like those seen in the normal, synaptically driven nerve. Figure 8 demonstrates that such desynchronization is possible. In this experiment a 5 kHz constant pulse train (conditioner) is started at time zero and a 1 kHz constant pulse train (stimulus) is started after 29 ms. The figure demonstrates the effect of increasing the conditioner amplitude. Note that at the highest conditioner amplitude, the alternating pattern is eliminated and a constant pattern results. The amplitude of the smooth responses are far higher than could be achieved with the conditioner alone, indicating that this conditioner/stimulus combination results in a larger pool of fibers being available to represent a modulated stimulus than would be available to represent modulation of a higher rate pulse train.

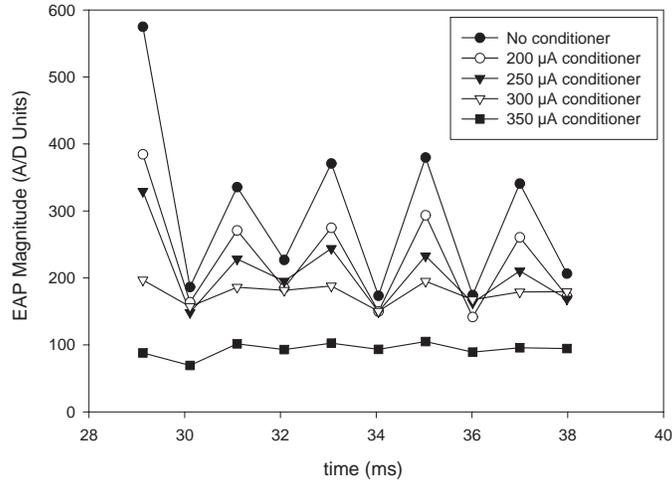


Figure 8: EAP N1P2 magnitudes from a human subject with a 5 kHz conditioner beginning at time zero and a 1.016 kHz stimulus beginning at 29 ms. Responses are measured to the stimulus. Courtesy of Blake Wilson and Charles Finley.

3.3 Implications

The ability to create pseudospontaneous activity is potentially of great importance and several patent applications are pending. The desynchronization provided by such activity may dramatically increase both dynamic range and temporal fidelity of the neural representation. Both simulations and preliminary experimental data from our laboratory, as well as the Research Triangle Institute support these claims. Pseudospontaneous activity restores many attributes of acoustic hearing in our simulations. Details will be provided in a later report but will be summarized here:

1. Dynamic range for a single fiber can be increased to 20-30 dB.
2. The normal relationship between spontaneous rate and threshold can be restored.
3. Period histograms for low frequency sinusoids can be made to appear virtually identical to those obtained acoustically.

4 Plans for the sixth quarter of this project

The following activities are planned for the sixth quarter (January - March, 1998) of this research project:

- Continue and extend studies of channel interaction using cat single-fiber responses.
- Expand the study of the EAP measured with multi-electrode arrays.
- Conduct model simulations in response to amplitude modulated pulse trains.
- Submission of a Phase II SBIR grant with Advanced Bionics. If funded, this would give the NPP contract access to a variety of multi-electrode array designs with which to study channel interactions.
- Begin experiments using triphasic waveforms.
- Complete a manuscript describing the driven properties of simulated fibers which have pseudospontaneous activity.
- Begin deafening of guinea pigs for studies of the EAP in chronically deafened animals.
- Prepare manuscript on single-fiber responses in cat.
- Present three posters and one podium presentation at ARO.
- Begin studies of single-unit responses to pulse trains.

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